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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/866,034	05/25/2001	David Botstein	P2930R1C1	4767

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EXAMINER	
SPECTOR, LORRAINE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/866,034	BOTSTEIN ET AL.	
	Examiner	Art Unit	
	Lorraine Spector, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *27 and 32-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *27 and 32-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/11/2005 has been entered.

Claims 27 and 32-35 are pending and under consideration.

Objections and Rejections under 35 U.S.C. §101 and §112

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 27 and 32-35 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well established utility for reasons cited in the previous Office Action mailed 2/9/2004 , at pages 2-4.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27 and 32-35 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants traversal filed 1/11/2005 has been fully considered but is not deemed persuasive.

To review prosecution briefly, the Examiner has made a *prima facie* case that the mild amount of gene amplification (approximately 2 fold) of nucleic acids encoding the claimed protein are not indicative of an increased amount of protein. References have been made of record by the Examiner to support the *prima facie* finding, including :

Sen, 2000, Curr. Opin. Oncol. 12:82-88, which teaches that a slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid.

Pennica et al. (1998, PNAS USA 95:14717-14722) who disclose that:

> "An analysis of *WISP*-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and overexpression, whereas overexpression of *WISP*-3 RNA was seen in the absence of DNA amplification. In contrast, *WISP*-2 DNA was amplified in the colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient."

It is the Examiner's belief that these references represent the state of the art.

In response to the rejections, applicants now argue several new references, which will be addressed individually. It is noted that applicants have not seen fit to make these references of record in an Information Disclosure Statement. Further, it is noted that applicants have redacted a portion of the Alitalo reference, at page 313.

Regarding the Lewin reference, as characterized by applicants, the reference teaches "various molecular events that lead of overexpression of a gene product". This argument has been fully considered but is not deemed persuasive because applicants are putting the cart before the horse. The issue here is *not* that a gene product has been found to be overexpressed, and an explanation of such is being sought, but rather that a *mild, two-fold* amplification of the DNA that would be transcribed to mRNA, that would be translated to protein. There is no evidence of record that the protein is present at elevated level, and the art would not lead to that expectation, as evidenced by Sen and Pennica. There is no assertion in the specification that a retrovirus has

been inserted upstream of the PRO1800 gene, nor would such be consistent with the data in the specification as originally filed. Similarly, there is no evidence of record of a chromosomal translocation, nor of any overexpression of the PRO1800 protein.

At page 4 of the response, Applicants assert that references by Alitalo and Merlino support the assertion that the claimed PRO1800 protein would have diagnostic utility. As characterized by applicants, "Alitalo teaches gene amplification of oncogenes results in elevated expression of the gene, and that increased dosage of the gene product may contribute to the progression of some cancers." This argument has been fully considered but is not deemed persuasive because once again, applicants are putting the cart before the horse. Alitalo is examining the amplification of *known oncogenes,* whose products were *known* to be overexpressed at the protein level. Further, dmils and HSRs, as discussed by Alitalo, are cytological phenomena. As stated by Alitalo at page 306, "Although the sampling of tumours is at present small, the finding of *known cellular oncogenes* among amplified DNA represented by dmil:s and HSR:s of cancer cells is provocative. Amplification has been found to affect at least five out of twenty *known* cellular oncogenes and the degree of gene amplification varies from *five to many hundred-fold* over the single haploid copies found in normal cells" (emphases added). Thus, Alitalo is discussing *known* oncogene, wherein the DNA is amplified *five to many hundred fold.* PRO1800 is neither a known oncogene, nor amplified five to many hundred fold. There is nothing in Alitalo's disclosure that would lead the artisan to conclude that a gene that is amplified two-fold in some cancers either would be expected to be an oncogene, nor would be expected to be accompanied by an increase in protein levels. With respect to the Merlino publication, EGF, or Epidermal Growth Factor, is a known growth factor. It is known in the art that overexpression of growth factors or their receptors can result in uncontrolled cell growth, one of the hallmarks of cancer. On the contrary, PRO1800 is asserted in the specification to have (unspecified) homology to Hep27, which Hep27 is a member of the short chain alcohol dehydrogenase protein family (page 2). There is no nexus between short chain alcohol dehydrogenases and cancer, nor is there sufficient similarity between PRO1800 and short chain alcohol dehydrogenase protein family such that the person of ordinary skill in the art would accept the assertion that PRO1800 is a short chain alcohol dehydrogenase. Further, Merlino discloses that the EGF receptor gene was amplified 4-5 fold, not the mere two-fold amplification

observed for PRO1800. Further still, the EGF receptor was *known to be overexpressed* in the cell line studied by Merlino. Applicants have provided no evidence of overexpression of the PRO1800 protein in any of the tested cancer cells.

At page 4 of the response, applicants argue that Bahnassy et al. "studied the amplification of *cyclin D1, cyclin A, histone A3* and *Ki-67*", and found "a significant correlation between *cyclin D1* gene amplification and protein overexpression." This argument has been fully considered but is not deemed persuasive. First, based upon applicants argument alone, we may presume that *no* significant correlation was found for the other genes studied, such that taken on applicants characterization alone, there would appear to be only a 25% chance of such a correlation (not that four is a significant sample size). More to the point, however, all four genes were selected by Bahnassy due to their known functions as 'cell cycle checkpoints', i.e. genes that influence the progression of the cell cycle. As cancer is known to be associated with aberrations in regulation of the cell cycle, this was a targeted study, looking at genes *likely* to be associated with cancer. No such association exists for PRO1800. Further, Bahnassy found amplification of the cyclin D1 gene to be 2-10 fold, higher than found for PRO1800. Finally, the discussion section of the paper clearly indicates that the art at the time the paper was written had *not* found either consistency or consensus on the assertion that amplification of cyclin D1 as associated with increased protein levels. In fact, at page 20, Bahnassy states that "So far, several studies were done to reveal the prognostic significance of cyclin D1 overexpression in various carcinomas, including CRC 1221. However, these studies yielded conflicting results which could be attributed to organ heterogeneity. In our study, patients with tumors that exhibited cyclin D1 overexpression tended to have poor prognosis." In all, Bahnassy shows that far more experimentation is required than is present in this specification as originally filed to establish a correlation between protein expression and cancer in the mind of the skilled artisan, and that the type of experimentation found in the specification as originally filed, in which a mere two-fold amplification of DNA was observed in a few cell lines, and no analysis of protein expression was performed, falls far short of the standard in the art. The Blancato reference, as for Lewin, examined a protein, c-myc, the same as discussed by Lewin, *known* to be associated with cancer. Blancato's starting point was that the protein was known to be overexpressed, and the

investigation was aimed at determining the mechanism of overexpression. No such overexpression has been established for PRO1800.

At page 5, applicants argue that it is well known in the art that initiation of transcription is the most common point for a cell to regulate the expression of each of its genes. This argument has been fully considered but is not deemed persuasive because the amplification of PRO1800 was demonstrated at the DNA level; there has been no examination of transcription levels of the gene, much less amounts of protein.

The Examiner notes additional art that supports the rejection, in that the art indicates that a two-fold amplification at the DNA level would not be expected to be predictive of protein amplification.

Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than l-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Hanna et al. (Pathology Associates Medical Laboratories, 1999) show that gene amplification does not reliably correlate with polypeptide over-expression, and thus the level of polypeptide expression must be tested empirically. The instant specification does not provide this additional information, and thus the skilled artisan would need to perform additional experiments. Since the asserted utility for the claimed polypeptides is not in currently available form, the asserted utility is not substantial.

Orntoft et al. (Molecular and Cellular Proteomics1:37-45, 2002) *could only compare the levels of about 40 well-resolved and focused abundant proteins."* (See abstract.) It would appear that applicants have provided no fact or evidence concerning a correlation between such low levels of amplification of DNA, found only in a minority of tested tumors which were not

characterized on the basis of those in the Orntoft publication, and an associated rise in level of the encoded protein.

Hyman (Cancer Research 62:6240-6245) found 44% of *highly* amplified genes showing overexpression at the mRNA level, and 10.5% of *highly* overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate. Further, the article at page 6244 states that of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification. This proportion is approximately 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO1800 would be correlated with elevated levels of mRNA, much less protein. Hyman does not examine protein expression.

Thus, the preponderance of the art supports the *prima facie* finding that a minor amplification of DNA would not form the basis for a substantial assertion of an association between PRO1800 protein and cancer.

Conclusion

No claim is allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Lorraine M. Spector. Dr. Spector can normally be reached Monday through Friday, 9:00 A.M. to 3:00 P.M. at telephone number 571-272-0893.

If attempts to reach the Examiner by telephone are unsuccessful, please contact the Examiner's supervisor, Ms. Brenda Brumback, at telephone number 571-272-0961.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Official papers filed by fax should be directed to 571-273-8300. Faxed draft or informal communications with the examiner should be directed to ***571-273-0893.***

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lorraine Spector, Ph.D.
Primary Examiner